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Review

Research into Fluorinated Pyrethroid Alcohols—an Episode in the History of Pyrethroid Discovery*

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Abstract: An account of pyrethroid research from 1975 to 1985 at Bayer AG is given. The exploitation of fluorine chemistry for this purpose led to increased activity of known 3-phenoxybenzyl pyrethroid esters and to the commercialisation of the broad-spectrum insecticide cyfluthrin, the particularly tick-toxic flumethrin and the rapid-acting household insecticides fenfluthrin and transfluthrin. The last two constituted in 1976 a novel type of pyrethroid, based on polyfluorinated benzyl alcohols, off the mainstream of published pyrethroid research. Transfluthrin, the single isomer (1*R*)*trans*-permethric acid ester of 2,3,5,6-tetrafluorobenzyl alcohol has just been introduced to the market. The history of its discovery and structure–activity data as well as resistance considerations regarding cyfluthrin, are presented. © 1998 SCI.

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Key words: pyrethroids; fluorinated; benzyl alcohols; knockdown activity; cypermethrin; transfluthrin; cyfluthrin

1 INTRODUCTION

1.1 Pre-pyrethroid research at Bayer

Research into insecticides at Bayer has extended over more than 100 years starting in 1892 with dinitrocresols (**1,** Fig. 1) used against the Gipsy moth *Porthetria dispar* L. In the 1930s the field of organophosphates was successfully opened up by Gerhard Schrader, Bayer, where 40% of all commercial developments in that class have been accomplished. This was followed in the 1950s by early engagements in the then new class of carbamates as well as in the early 1970s with the new benzoylureas. Another important area of international insecticide research was the organochlorine compounds, but Bayer was never involved with these materials. Many companies were engaged in the organophosphate and carbamate fields resulting in a large number of patents being taken out over the period 1935–1990.[1] Parathion (1948) and tebupirimfos (1996) were the first and last organophosphorus compounds to be marketed by Bayer (**2** and **3,** Fig. 1, respectively). Synthesised by Fritz Maurer in 1982,[2–4] the high intrinsic activity of tebupirimfos enables it to be used as a low-concentration granular formulation which provides safety to birds and very good control of corn rootworm (*Diabrotica* spp) at 200 g ha^{-1}. Propoxur (1964) and

* Based on the awardee lecture given at the 1996 ACS International Award for Research in Agrochemicals Symposium, Orlando, USA, 1996 and dedicated to K. H. Büchel on the occasion of his 65th birthday.

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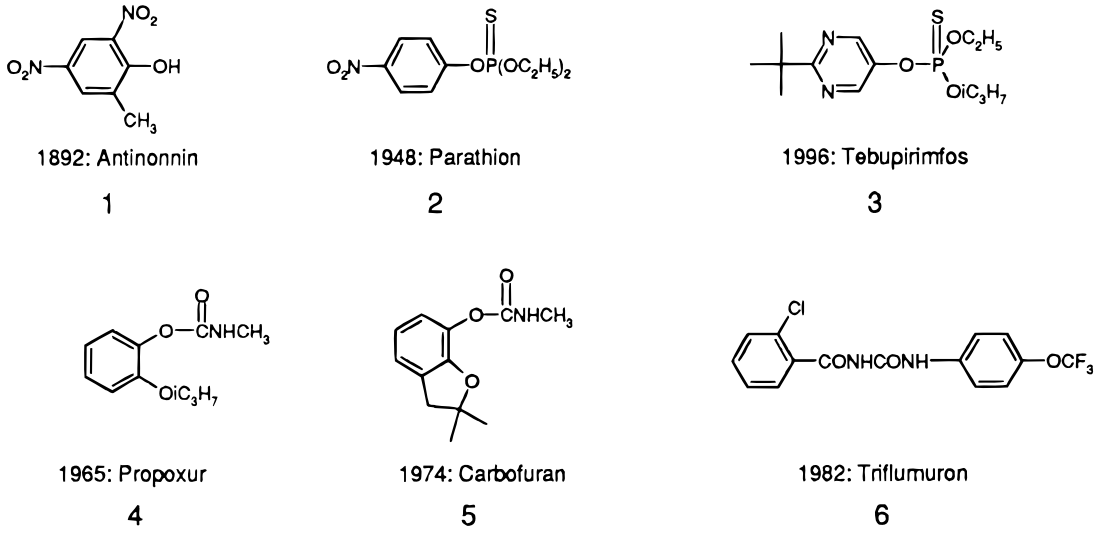


Fig. 1. Some important introductions to the insecticide markets from pre-pyrethroid research in Bayer AG.

carbofuran (1974) (**4** and **5,** Fig. 1, respectively) are examples of carbamates from Bayer which have been used successfully for the control of household insects and soil pests, respectively.

The large number of patent applications submitted for benzoylurea insecticides between 1970 and 1987 demonstrates the great international research efforts in this area, but the commercial yield has not been proportionate to the research input. At Bayer, Walter Sirrenberg synthesised more than 10 000 benzoylureas, (pers. commun.) and triflumuron (**6,** Fig. 1; 1982) resulted from these efforts. However, the lesson from the vast input in the benzoylurea field is that not every biological mode of action can be translated into the real world of crops and their parasitic insects.

2 AN EARLY APPRAISAL AND BELATED ENGAGEMENT IN THE PYRETHROID FIELD

Our initial approach to the structurally more complex pyrethroid insecticides suggested that 'normal' application rates of about 1 kg ha^{-1} and the apparent photolability of compounds of this class would make them much too expensive and technically unsuitable for agricultural purposes, so that they would have no commercial relevance.

However, Michael Elliott's 1974 publication[5] on permethrin and deltamethrin, which showed insecticidal activity of a new order of magnitude combined with photostability, brought us into the field quite late, as shown in Table 1. It seemed that all the good claims had been made already and even that all the licences had been sold! Nevertheless, Bayer did become involved in this field and this review records our successful work in this area and how it progressed between 1975 and the early 1980s.

2.1 The mapping of a putative pyrethroid binding site

This was approached in several ways. The first was an investigation of the effect of fluorine substitution in the already outstandingly active cypermethrin molecule (**7,** Table 2); such molecules were not then covered by patents.

Rainer Fuchs in Schrader's laboratory building in Wuppertal used a method for the formation of an aromatic C–F bond by decomposition of triazenes of general formula $R_xC_6H_yN=N(CH_3)_2$ in hydrogen fluoride (HF), because his colleague Heinz Förster was acquainted with triazene chemistry for a cancerostatic project. Hans Klusacek in the Leverkusen fluorine laboratory optimised the Wallach reaction, first reported in 1880, using liquid HF.[6] In cooperation with Erich Klauke, head of the fluorine laboratory in Leverkusen, Fuchs produced all seven possible isomers of fluorinated cypermethrin (**8–14,** Table 1) and it was found that activity was improved only with the 4-fluoro derivative (**9**), and that it was almost eliminated when chlorine was substituted for fluorine in this position. The 4-fluoro compound,[7,8] named cyfluthrin (**9,** Table 1), did not show this improved activity over cypermethrin for all insects (Table 3) but laboratory results were sufficiently promising to proceed with field trials. Meanwhile, the author, then in the plant protection research of the main laboratory in Leverkusen, using the olefinic component (**15,** Fig. 3) synthesised by Rainer Lantzsch in the same building, had succeeded in preparing the permethric acid (dichlorovinyl acid, DV-acid) (**16,** Fig. 2) by the diazoester method on the kilogram scale in his laboratory for field trials of cyfluthrin and was seeking patentable new esters of this compound. In common with workers in competitor organisations, the work of Michael Elliott at Rothamstead and of colleagues at Sumitomo was studied carefully to understand structure–activity relations. We made an attempt to

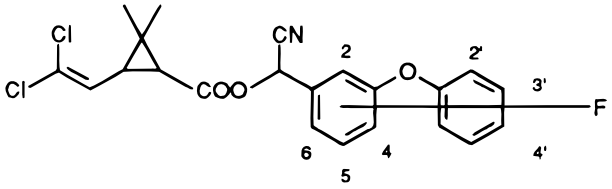
TABLE 1

Patent Applications for Pyrethroid Insecticides (Active Ingredients) in Priority Years 1949–1988.

Number of patents for pyrethroid active ingredient in year 19??																																
87	*86*	*85*	*84*	*83*	*82*	*81*	*80*	*79*	*78*	*77*	*76*	*75*	*74*	*73*	*72*	*71*	*70*	*69*	*68*	*67*	*66*	*65*	*64*	*63*	*62*	*61*	*60*	*58*		*57*	*49*
																												1	1	1	Boyce-T,[a]
3	4	4	7	10	9	5	6	16	11	8	2	1	5	3	5	3	7	4	6		3	2	1	6	1	1	Sumitomo				
		2	1	1			2	1	2	1	1	2		2	1		1	1		7	4	2			2	Dainippon					
			5		4	2			1	2	1		1	1	5			1				5		1	NRDC						
										1						1			1					1	Hoffmann-LaRoche						
1	3	5	3	5	22	16	5	5	4	1	2			2	1			2			1	Roussel-Uclaf									
																2		5			1	Taisho									
															2			1	6	14	Yoshitomi									
			2	3	1	4	5	7	6	1		1		3	1		1			2	Katsuta									
								1		2	1		1	2	3			1	1	Sankyo										
	1	2	1					1	1	1					1	1			1	BASF										
																3	3	Procter & Gamble												
																2	2	Fumakilla												
														1		1	Johnson													
			2			6		14	8	7	3	2	1	3	1	1	Shell													
1	3	2	1	1	2	6	1	8	12	9	13	5	1	Ciba-Geigy																
1	9	7	2	1	2	2	3	3	2	2	1		1	ICI																
									3	2	2	1	ACC																	
			3		2	3	2	2	2	1	1	1	CSIRO																	
					1	1	13	14	2	2	2	Kuraray																		
1		2		1	4	7	6	10	9	5	3	Bayer.																		
	1		3	3	3	4	8	3	10	1	1	FMC																		
						1	3	6	4	3	1	Nissan																		
			1				5	9	3	3	Zoecon																			
					1		2	2	2	1	Montedison																			
							1		1	1	Chinoin																			
							2	2	2	1	Mobil																			
						1		6		1	Dow																			
										3	Stauffer																			
								1	1	Sorex																				
						1	1	1	Union Carbide																					
						1	2	1	Nippon Soda																					
						3	5	3	Mitsubishi																					
	2	6	3	3	2	2	2	Mitsui Toatsu																						
1	1	2					2	Hoechst																						
		1	1			1	DuPont																							
			1	1	Cheminova																									
	3	6	1	1	Schering																									
			1	1	Union Explosivos																									
		1	1	Kureha																										

[a] Names underlined possess proprietory pyrethroids.

TABLE 2
Influence of Position of Fluorine Substitution in Cypermethrin on Mortality of *Spodoptera frugiperda* Larvae



Compound	*Position of F*	LC_{95}[a] (*mg litre*$^{-1}$)	*Name*
7	none	5	Cypermethrin
8	2	50	
9	4	1	Cyfluthrin
10	5	5	
11	6	100	
12	2′	10	
13	3′	10	
14	4′	5	

[a] LC_{95} = Concentration for 95% mortality of test group.

map a putative pyrethroid binding site from their, and our own, data. This was done using an active/inactive analogue approach in order to arrive at the limits of the pyrethroid structure–activity space which allowed assessment of the maximum permissible volume of the alcohol and acid components without complete loss of activity of the pyrethroid, particularly DV-esters. It was hoped that this inverse strategy away from the known optimum would open the chance for the discovery of another new summit of biological activity.

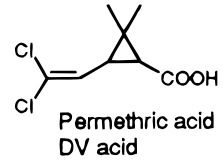
Results of this investigation into limits within which activity was achieved (Fig. 3) led to some surprises. We had shown that introduction of a positive charge at the 4′-position in permethrin (**19,** Fig. 3) by means of a quaternary ammonium group in compound **17,** (Fig. 3) abolished activity: however, a *bis*-tertiary amine synthesised by Fuchs by exchanging -CN in cypermethrin for an *N*-(*N*′-methyl)piperazinylmethyl group (**18,** Fig. 3) proved to be surprisingly active. This pyrethroid-octopaminoid hybrid had been envisaged from speculation on an octopaminergic connection in the symptomology of α-cyanopyrethroids, suggested by a lecture at the first Neurotox Conference in 1979.[9] A compound of structure **18** should be protonated to a positively charged species under the physiological conditions within a nerve.

Another very important factor for eliciting the spatial requirements for pyrethroid binding was the active conformation of the pyrethroid isomers. 'Flattening out' Elliott's optimal alcohol in permethrin (**19,** Fig. 3) indicated limited space availability in the horizontal extension of the *para*-position (Fig. 4); larger substituents caused a sudden loss of activity. The 4-benzyloxybenzyl

TABLE 3
The Fluorine Bonus in Cyfluthrin for Toxicity to Various Insects

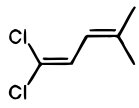
	Tetranychus urticae	Ceratitis capitata	Phaedon cochleariae	Plutella maculipennis	Spodoptera frugiperda	Mycus persicae	Euscelis bilobia
Fluorine bonus **f**[a]	23	5	2	5	1	25	

[a] Fluorine bonus $\mathbf{f} = \dfrac{LC_{50}\ \text{cypermethrin}}{LC_{50}\ \text{cyfluthrin}}$.



Permethric acid
DV acid

16



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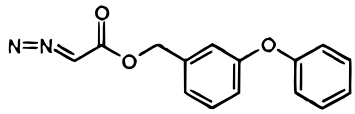

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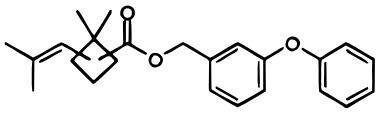

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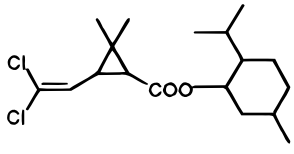

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(+/−) *trans*, I

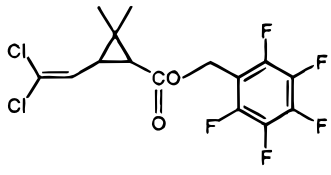

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Fig. 2. Some structures discussed in the text.

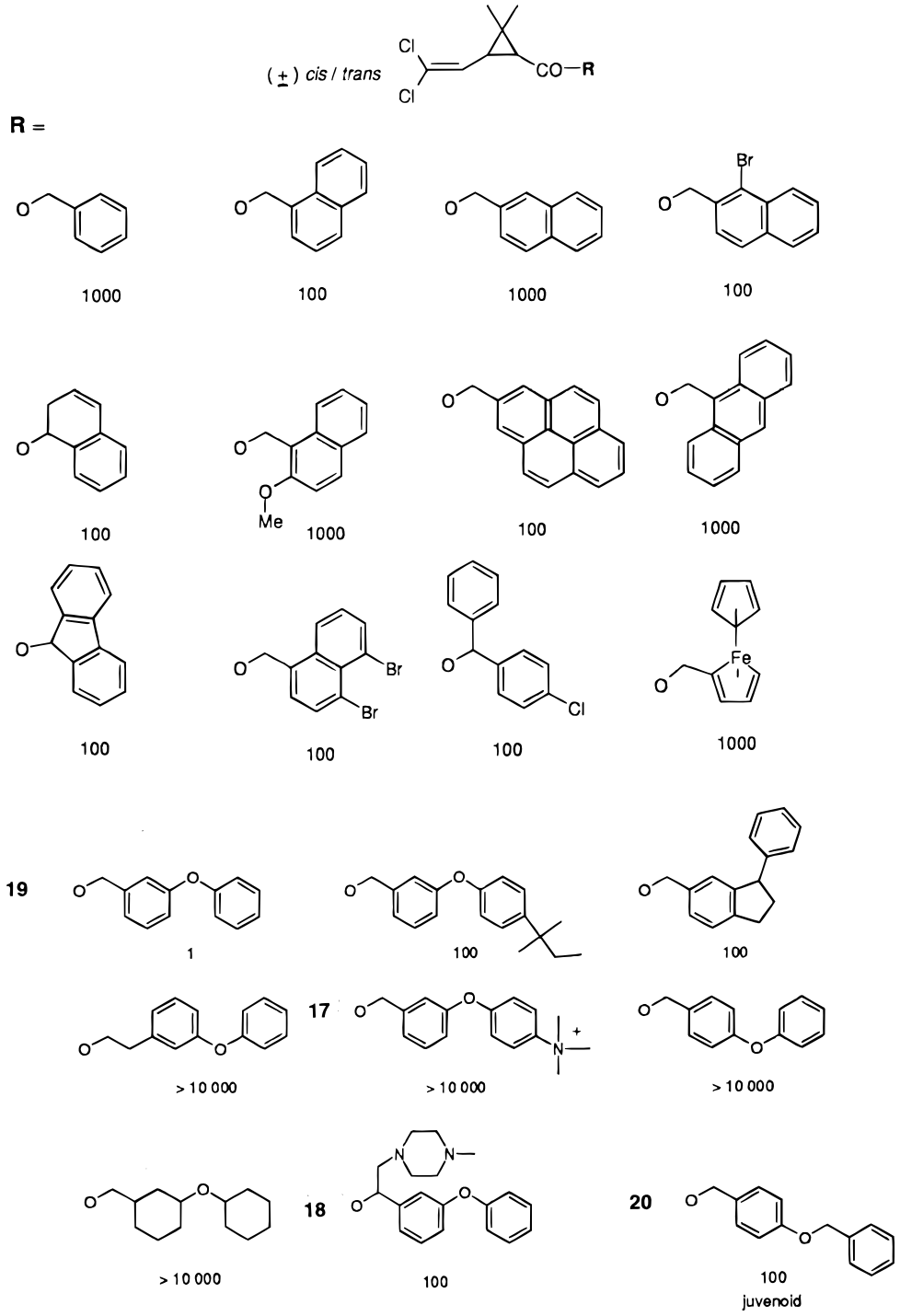


Fig. 3. Insecticidal activity of extreme sized alcohol components for DV-ester putative pyrethroid binding site mapping with LC_{95} values (mg litre^{-1}) for *Plutella maculipennis* larvae, leaf-dip bioassay.

ester (**20,** Fig. 3), designed to challenge our SAR hypothesis and expected to be inactive, provided new leads for our synthetic programme. When tested by Peter Roessler against *Spodoptera* spp larvae in his insect growth-regulator (IGR) tests it was observed that, after some time, the treated larvae moulted into supernumerary larval stages, which proved that the SAR-spaces of pyrethroids and juvenoids were neighbours. Thus a new mode of action was suggested. Less frustrating, and rather instructive in view of the active compounds from the literature, was the great number of inactive esters we prepared from *m*-phenoxybenzyldiazoacetic ester (**21,** Fig. 2) and open and cyclic olefins as well as aliphatic, phenolic and benzylic esters based on permethric acid (**16,** Fig. 2). Particularly rewarding for the understanding of this mode of action was the inactivity of all six racemates of the four-membered ring homologue of phenothrin (**22,** Fig. 2)[10]

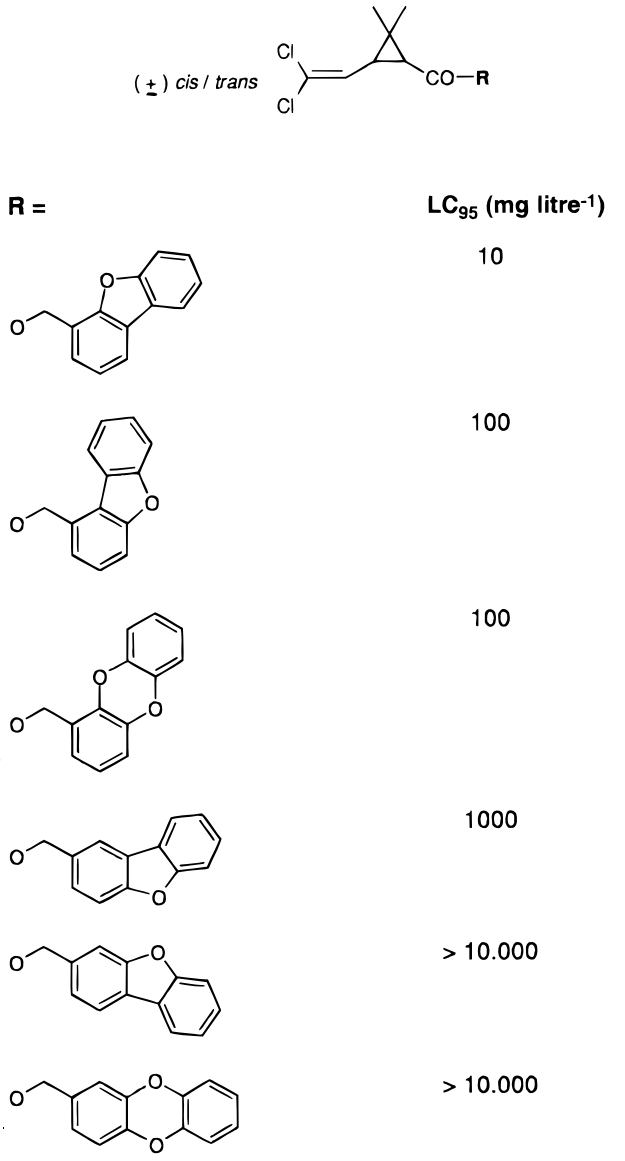


Fig. 4. Activities of flattened permethrin (**19**, Fig. 4) analogues against *Plutella maculipennis* larvae, leaf-dip bioassay.

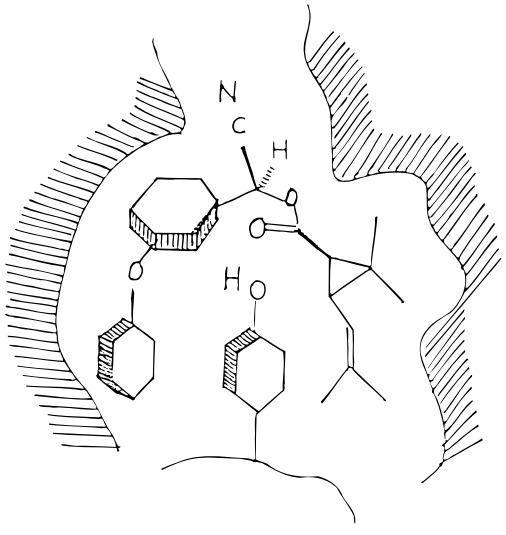


Fig. 5. Proposed active conformation of cypermethrin in the hypothetical pyrethroid binding site.

that we obtained by our cooperation with Scharff, Technical University Aachen. The stereochemical information derived from literature data and structural investigations, using simple mechanical molecular models, together with the insecticidal data derived from leaf-dip bioassays, suggested in 1977 that there could be a binding pocket for active pyrethroids in which the pyrethroid curves into a horseshoe shape, possibly clamping around an aromatic residue of the protein backbone. This explained to us why some structures were active and others inactive (Fig. 5). A similar 'horseshoe' model of another highly hydrophobic, flexible model juvenile hormone (JH111) was later proposed by M. Peter of the University of Bonn for the active conformation necessary for the compounds to be recognised and hydrolysed by JH111 esterase from *Locusta migratoria* L. on the basis of his work with JH111 and its analogues.[11]

Our model could be applied successfully to other compounds published subsequently in the literature[12,13] (Fig. 6). Moreover, X-ray analysis of a crystalline molecular complex (**23,** Fig. 7) of a certain diastereoisomer of our acaricide flumethrin (**33,** see Table 8) with 2,6-dimethylnaphthalene, a very minor component of the technical solvent 'Solvesso', isolated from a commercial tickicide formulation which had caused problems in the field, gave useful information about non-bonding interactions of pyrethroids with aromatic ligands.[14]

3 PENTAFLUOROBENZYL ALCOHOL

The author's work with synthesising new pyrethroid esters for screening involved the functionalisation of many methyl aromatics (Fig. 8). Work with the *m*-phenoxybenzyl, and other, systems indicated that electron-withdrawing substituents in *para*- and electron-donating substituents in *meta*-positions lead to deactivation in terms of the homolytic strength of the benzylic C–H bond, as occurs during radical chlorination or oxidation. We speculated that the C–H bond at the benzylic or allylic α-carbon, which is present in virtually all active pyrethroid esters, might play an important role for activity. Results from the screening of several analogues (Table 4) corroborated our impression that all active pyrethroid esters are of benzylic or allylic nature, that all active esters bear an α-*H*-atom and that all active esters are hydrophobic. This supported our hypothesis that hydrophobic, deactivated benzyl esters are more biologically active than esters of benzyl alcohols that are not deactivated with respect to the strength of this C–H bond. If this was true, then an isotope effect might be discernible, but our test system did not indicate a significant difference between α-dideuteropermethrin and permethrin itself. Nevertheless, we suspected that biologically highly active

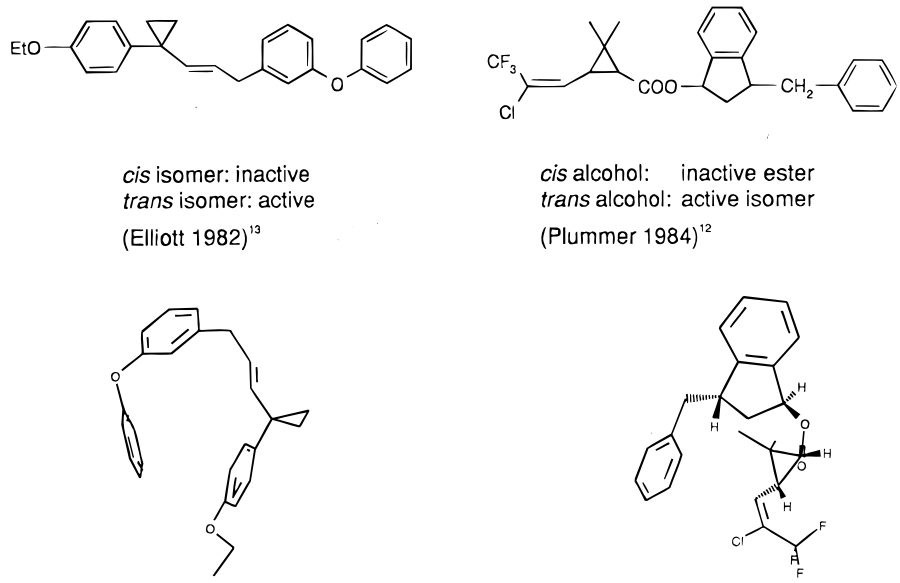


Fig. 6. Application of the 'horseshoe' model of active pyrethroid conformation to subsequent examples of unusual pyrethroid structures. Only the active *trans* isomers can adopt the proposed conformation.

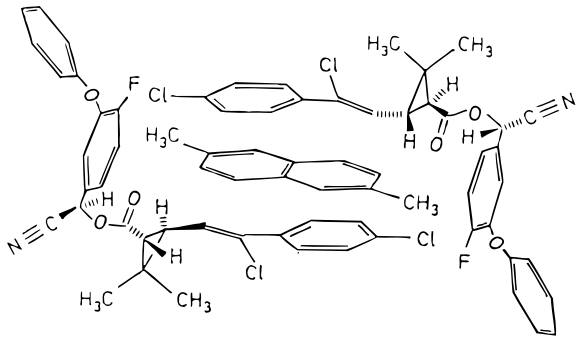


Fig. 7. X-Ray structure of a flumethrin-dimethylnaphthalene complex: non-bonding interaction of a pyrethroid with an aromatic moiety.

pyrethroid esters of highly deactivated and highly hydrophobic benzyl alcohols might exist. Investigation of a number of components having electronegative, but hydrophobic substituents, i.e. oligo- and poly-halogenated, and ultimately polyfluorinated, benzyl alcohols proved this to be the case.[15] Some esters of penta- and tetrafluorobenzyl alcohols are extremely fast-acting pyrethroids, especially against dipterous insects, as found by Wolfgang Behrenz in the household insecticide laboratory in Leverkusen. However, the most active compounds were esters of permethric acids. The (1*R*)*trans*-isomer of permethric acid pentafluoro-benzyl ester became the insecticide fenfluthrin (**24,** Table

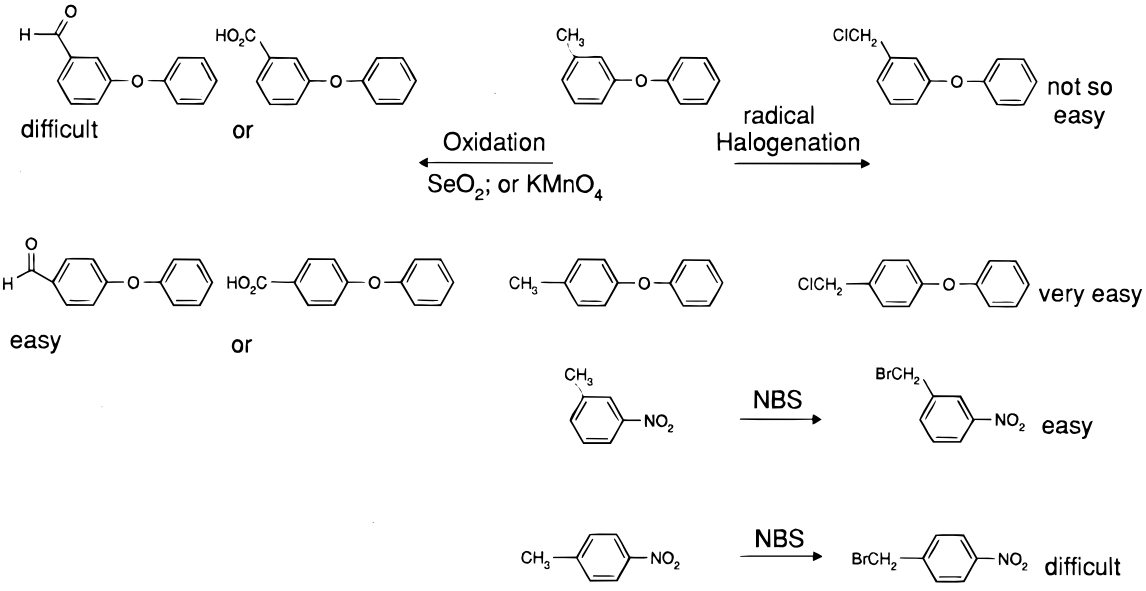
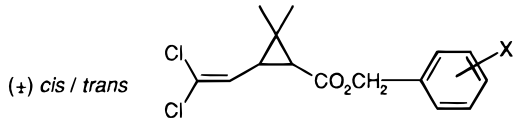


Fig. 8. Functionalisation of methyl aromatics by oxidation and halogenation: a *m*-phenoxy substituent or a *p*-NO_2 group deactivates the benzylic CH-bond; a *p*-phenoxy or *m*-NO_2 substituent activates the benzylic CH-bond.

TABLE 4
Comparison of Insecticidal Activities of DV-Esters of Isomeric Benzyl Alcohols



Order of activity[a]
X = 3-OC_6H_5 ⋙ 4-OC_6H_5
3-OCH_3 > 4-OCH_3
4-NO_2 > 3-NO_2
4-CF_3 > 3-CF_3

[a] Leaf-dip bioassay, screening of six insect species.

5)[16] but esters of other pyrethroid acids had much poorer activity (Table 5). In contrast to the esters of *m*-phenoxybenzyl alcohol, the *trans*-isomers were found to be as active as, or more active than the *cis*-isomers in terms of speed of action. The *cis*-isomer (**25,** Table 5) is much more active against rats and soil-borne insects, but development of this compound was abandoned for economic reasons in the late 1970s. The 2,3,5,6-tetrafluoro esters are considerably faster-acting than the 2,3,4,5-trifluoro ester. The less-fluorinated esters and chlorofluorinated esters are less active and slower-acting (Table 6). Winfried Flucke in the Toxicological Institute at Wuppertal found a huge difference in acute toxicity to rats between the *para-H*-tetrafluoro ester of (1*R*)*trans*-DV acid and that of the (1*R*)*cis*-isomer, 5000 mg kg^{-1} p. o. compared with 20 mg kg^{-1}. This difference, and the opportunity to use the expensive alcohol component, known since 1968,[17] only for the active isomers, led to the decision to develop transfluthrin (**32,** Table 7).[18,19] This involved biological activity and application studies by Klaus Mrusek in the new household insecticide laboratory in Monheim and the devising of a technical process for the manufacture of the alcohol component by Ernst Kysela in the central research laboratory in Leverkusen.

4 PYRETHROIDS AND PENTAFLUOROBENZYL ALCOHOL—A HISTORICAL REVIEW

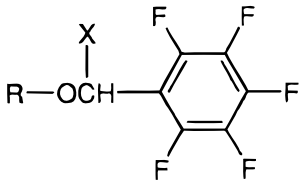
Fenfluthrin (**24,** Table 5), found in 1976, resulted in retrospect from the esterification of the known compounds 2,3,4,5,6-pentafluorobenzyl alcohol[20,21] and permethric acid (**16,** Fig. 2).[22,23] While MacBee (Purdue University) was working with pentafluorobenzyl alcohol, Barthels, whose laboratory at Cornell was a mere 500 miles away, was synthesising a chlorinated methylenedioxybenzyl chrysanthemate which was subsequently commercialised (Barthrin). Table 7 shows that a 1962 patent application by the Japanese company DaiNippon[24] formally encompassed a larger area of pyrethroids (**26,** Table 7), but they were interested in polymethylbenzyl esters and not in the polyhalo analogues. Elliott already had pentafluorobenzyl chrysanthemates (**27,** Table 7) which he made as derivatives of the very scarce pentafluorobenzyl alcohol, presumably donated to him by Tatlow of the University of Birmingham, UK for use as a standard in the GC analysis of the corresponding chrysanthemic acids.[25] Apparently, Elliott pursued exclusively the allylbenzyl lead derived from natural pyrethrin[26] and did not include this GC standard in his insecticide tests, so he missed the high insecticidal activity and very rapid action of this compound against adult mosquitoes. In the 1960s Sumitomo were concentrating upon chrysanthemic esters[27] of polychlorobenzyl alcohol, such as **28** (Table 7), which are considerably less active than the corresponding permethric acid esters (**30,** Table 7). The latter were claimed subsequently by Dr Aries at his desk in Paris as a result of studying patentable loopholes at the same time as we were becoming involved with pyrethroids. His patent was published[28] at the same time as my colleagues Erich Klauke and Albrecht Marhold in the central research fluorine laboratory Leverkusen were involved in preparing polychlorofluoro- and polyfluorobenzoic acids according to my requests, which was very expensive chemistry! However, results from biological screening tests in our household insecticides laboratory and laboratory for agricultural insect pests, August 1976, proved very encouraging.

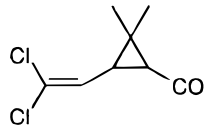
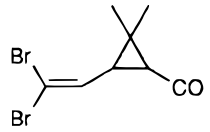
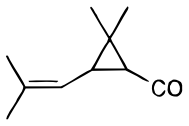
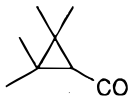
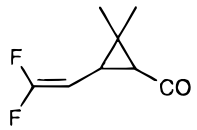
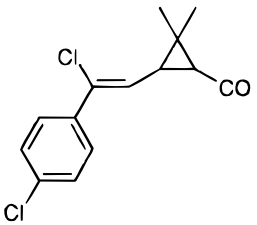
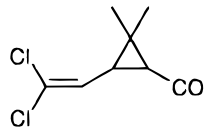
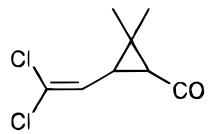
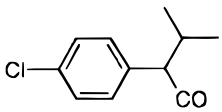
Two years later, Martyn Ford's group at Portsmouth, UK, including pentafluorobenzyl pyrethroids (**24,** Table 7) as part of their QSAR work on pyrethroids,[29] immediately recognised the importance of this (re)invention. Our patent application, published at this time,[15] aroused considerable in-house scepticism regarding the technical feasibility and economic margins of pyrethroids based on polyfluorobenzyl alcohols. A gap in the field of polyfluorobenzyl pyrethroids was later filled with a contribution from Huff and Punja at ICI.[30] They were seeking a volatile pyrethroid which would be useful as a fumigant and their work resulted in the marketing of tefluthrin (**31,** Table 7). This compound successfully controls a wide range of soil insect pests in maize, sugar beet and other crops.

In the mid-1970s there was much interest within the agrochemical industry in polyfluorinated derivatives of potentially active molecules. Over the next ten years the periphery of the pyrethroid base structures was also probed with small polyfluoro clusters (Fig. 9) which led to a number of promising, or even successful, compounds. It turned out that polyfluorobenzyl alcohols are one of five subtypes of alcohol components (seven alcohols of commercial value) with optimal structures for very high insecticidal activity of pyrethroid esters (Fig. 10).

For Bayer, as a belated starter in the pyrethroid com-

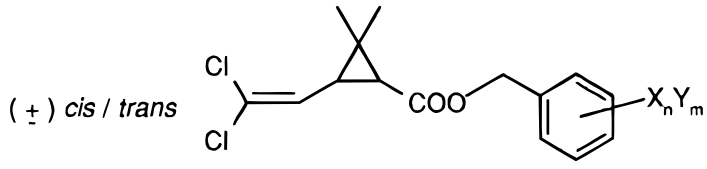
TABLE 5
Rank of Insecticidal Activity of Pentafluorobenzyl Pyrethroid Esters

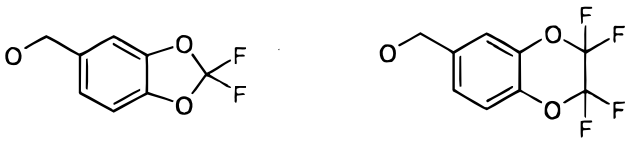


X	R	activity range (mg · litre^{-1})
H	 1*R trans* > 1*R cis* **24** Fenfluthrin **25** NAK 1654 NAK 1901	1
H		10
H		
H		
H		
H		100
CH_3		1000
CN		> 1000
H		

[a] Leaf-dip bioassay, screening of six insect species.

TABLE 6
Ranking of Insecticidal Activities of DV-Acid Polyhalobenzyl Esters



X, Y				Activity Range (mg · litre^{-1})
2,3,5,6 F_4	4 F			1
	4 CH_3			
	4 H			
	4 SCH_3			
2,4,5,6 F_4	3 Cl	> 3,4,5,6 F_4	2H	10
2,3,5,6 F_4	4 SC_2H_5	> 2,4,6 F_3	3,5 Cl_2	
2,3,4,5,6 Cl_5		> 2,3,5,6	Cl_4 4H	
F_{1-3}; Cl_{1-3}; $(CF_3)_{1-3}$ 				100
Benzyl				1000

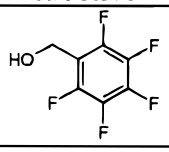
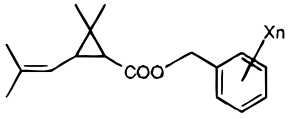
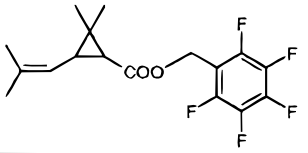
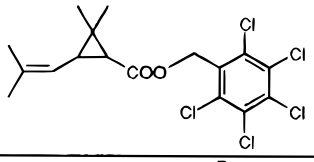
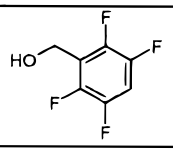
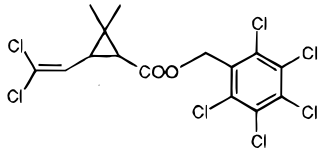
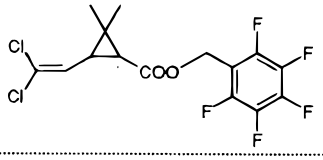
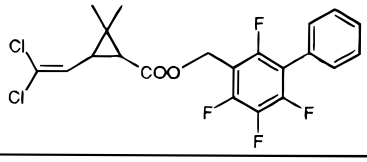
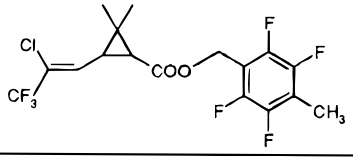
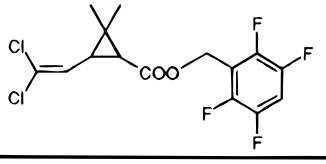
[a] Leaf-dip bioassay of six insect species.

petition, the exploitation of fluorine chemistry proved to be the key to a finally successful campaign in the shade of the mainstream pyrethroid research. It led to the discovery of broad-spectrum cyfluthrin (**9,** Table 8) and to flumethrin (**33,** Table 8), from Rainer Fuchs' laboratory, which is particularly active against ticks, and to the relatively volatile, rapidly acting household insecticide transfluthrin (**32,** Table 8) from the author's. The outcome world-wide of pyrethroid research is summed up in Fig. 11. In the aftermath of our relatively limited engagement in pyrethroid research, which was largely terminated about 1982, three review books on pyrethroid research from the author's desk have been published.[31,32]

5 TECHNICAL STEREOCHEMISTRY

A technically feasible method for resolution of DV-acid into its 1*R* and 1*S* forms, based on a technically available, optically active, pure auxiliary compound was an obvious goal. Of the few auxiliary compounds available on a tonne scale, L-menthol, familiar to the author from his work in K. Mislow's laboratory in Princeton,[33,34] yielded nicely crystalline (1*S*)*trans*- or (1*S*)*cis*-ester, the unwanted ones (**34,** Fig. 2)! At the same time, Elliott[35] separated the four diastereoisomers by chromatography, but this would not be feasible as an industrial method. However, it was discovered that D-menthol was recycled in technical quantities in Bayer's L-menthol production, so the road was now open for the manufacture of large quantities of (1*R*)*trans*-DV acid and it was decided to go ahead with production of the single optical isomer pyrethroid, transfluthrin (**32,** Table 8). Unfortunately, all attempts to achieve economically attractive isomerisation of the unwanted (1*S*)*trans*-DV acid to the *trans*-racemate or to the all-isomer mixture failed. Total photochemical racemisation[36] can only be achieved in an asymptotic fashion, while *cis*/*trans* equilibrium is reached earlier, depending on the solvent (K. Naumann, G. Heine, 1980, unpublished). This is understandable by the assumption of radical cleavage of all bonds in the cyclopropane moiety (Fig. 12). Treatment

TABLE 7
History of Polyfluorobenzyl Alcohol and Pyrethroid Chemistry

compound	structure	year	names	comment
		1951 1961	Mc Bee Tatlow	first synthesis pure compound
26		1962	Dainippon	X = Alkyl, Halogen n = 1-5
27		1963	Elliott	GC derivative
28		1966	Sumitomo	insecticide
29		1968	Stephens	first synthesis
30		1974	Aries	insecticide filed Nov. 74 open May 76
24		1976	Naumann	insecticide filed Dec. 76 open Oct. 78
	same compound	1978	Ford	QSAR Autumn 78
		1978	Plummer	insecticide filed Dec. 78
31		1979	Huff	insecticide filed Feb. 79 ± *cis*
32		1985	Naumann	single enantiomer 1*R trans*

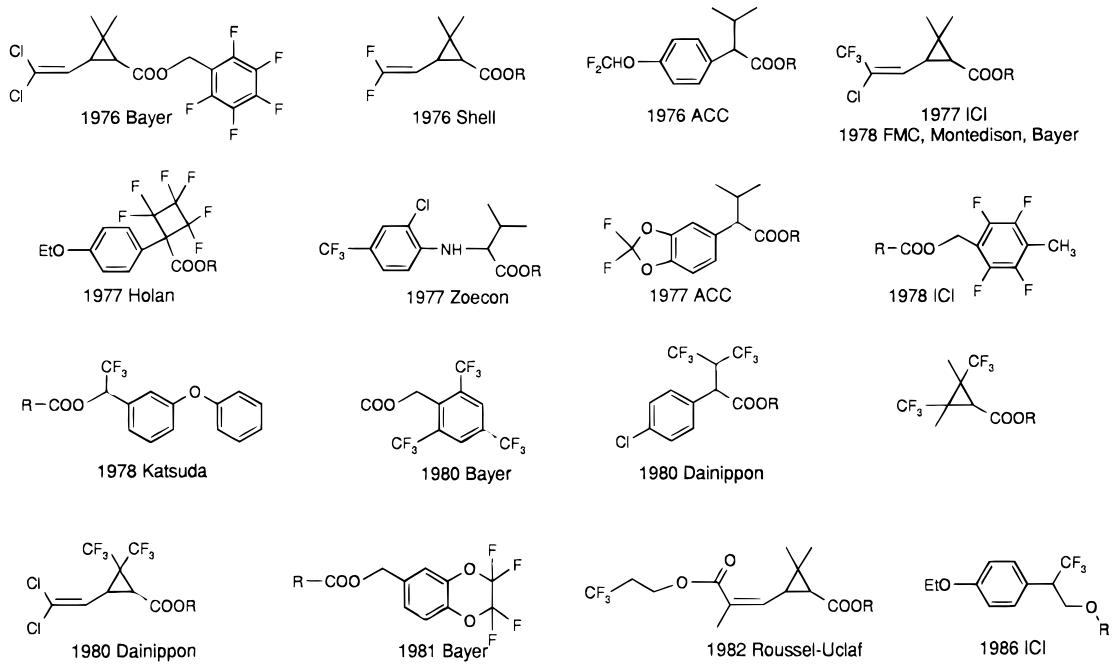


Fig. 9. The polyfluoro clusters in pyrethroid research.

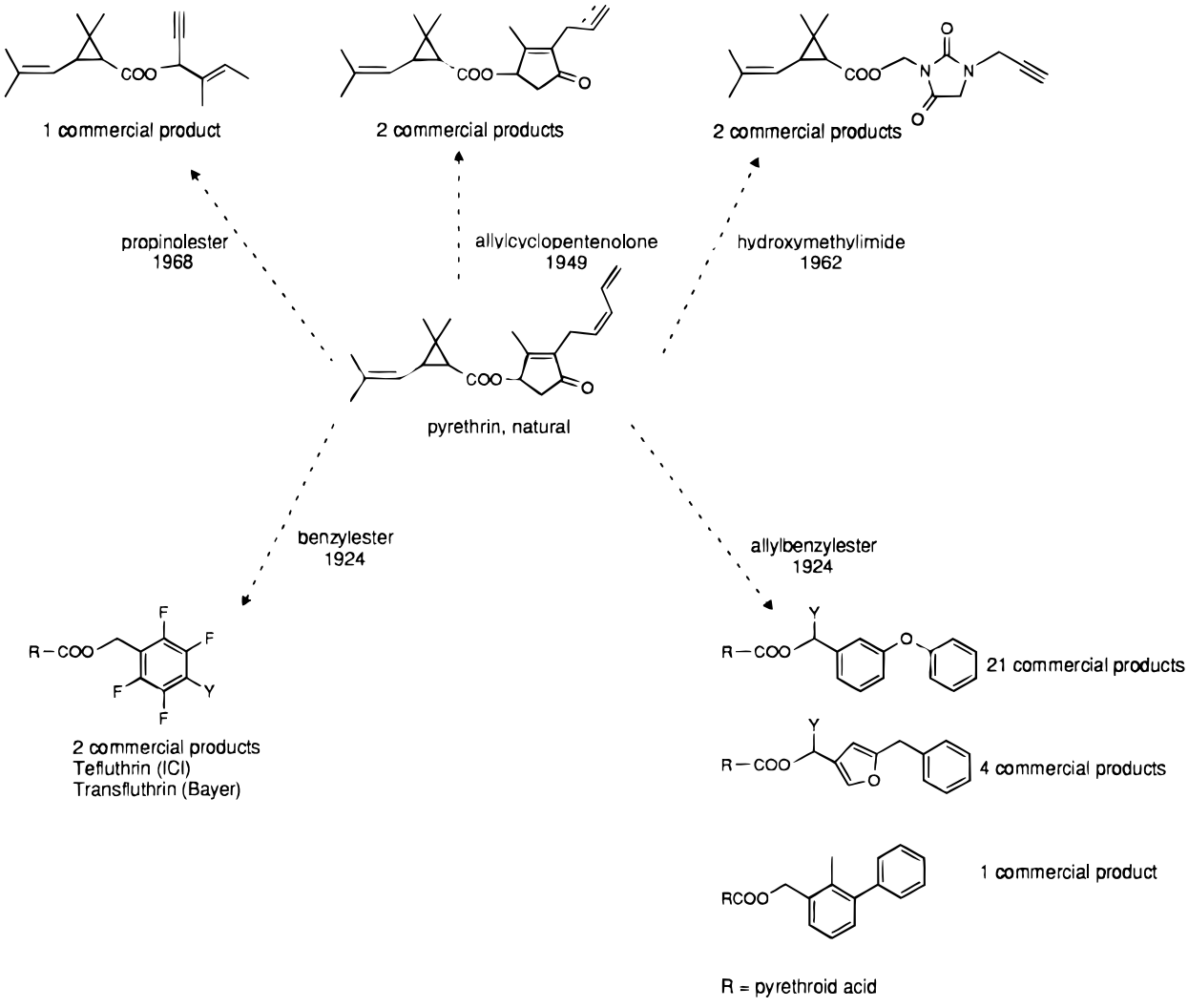
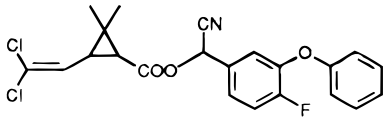
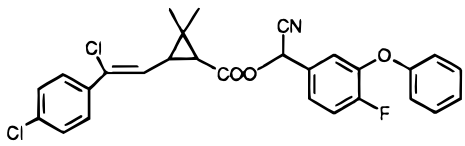
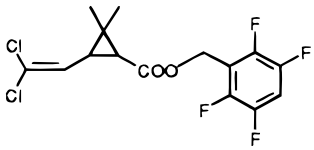


Fig. 10. Evolution of five optimal pyrethroid alcohol subtypes from the natural lead compound pyrethrin.

TABLE 8
Bayer's Commercial Proprietory Pyrethroids

Compound	*Common name*	*Formula*	*% Active isomers*	*Use*
9	Cyfluthrin		20	Broad acting insecticide
35	Betacyfluthrin		50	(residual activity)
		(±) *cis/trans*		
33	Flumethrin		25	Ticks
		(±) *trans, Z*		
32	Transfluthrin		100	Hygiene knock-down insecticide
		IR trans		(little residual activity)

of the acid chloride by heat or iodine to give the (1*R*)*cis*/(1*S*)*trans* or a non-racemic mixture of all isomers respectively, did not solve the problem either (Fig. 13). Therefore the cheapest method of disposing of larger amounts of the unusable optically active manufactured waste proved to be incineration!

6 RATIONALISATION OF THE APPARENT LOWER RESISTANCE FACTORS FOR CYFLUTHRIN

The build-up of resistance to pyrethroids in insects was always a possibility. However, research which started ten years ago revealed that *Musca domestica* L. and other insects had very low resistance factors against fenfluthrin and other polyfluorobenzyl pyrethroids, in contrast to the *meta* phenoxybenzyl pyrethroids[37–39] (Table 9). This resistance is caused mainly by selection of surviving insects which have different pyrethroid binding sites (knock-down resistance, KDR), by higher capacity for detoxification by metabolic oxidation or by hydrolysis, or even through sequestration by specific proteins. Thus, fenfluthrin and transfluthrin still interact with those 'new' sodium channels of the resistant insects and/or they do not interact so much with the 'new' detoxifying enzymes. Also, these polyfluorobenzyl pyrethroids have a strategic advantage over the *meta*-phenoxybenzyl esters due to their lack of extended residual activity. The late Roman Sawicki (Rothamsted) showed[40] that insecticides with less persistance could be used repeatedly to give satisfactory control without causing resistance. On this basis, the less persistant

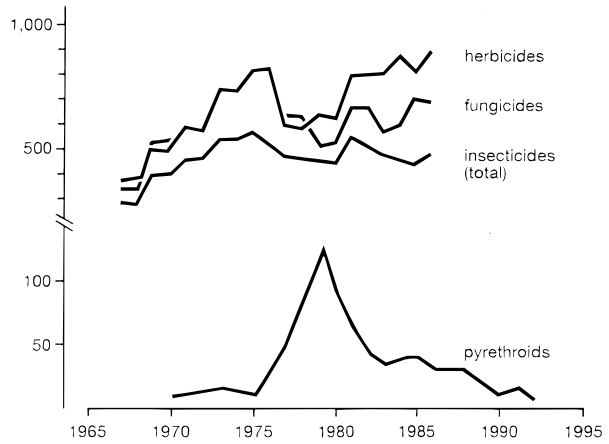


Fig. 11. Pyrethroid research and research for new active ingredients for plant protection (number of annual patents; year of priority).

TABLE 9
Resistance Factors against the Fluorinated Pyrethroids Cyfluthrin and Fenfluthrin compared with Cypermethrin

Compound	*Resistance factor*[a] Musca dom. *super kdr.*	Heliothis arm. *oxidase res.*
Cypermethrin	5100	25
Cyfluthrin	240	13
Fenfluthrin	42	0·5

[a] Resistance factor = LC_{50} resistant strain/LC_{50} susceptible strain. See Refs 37, 42.

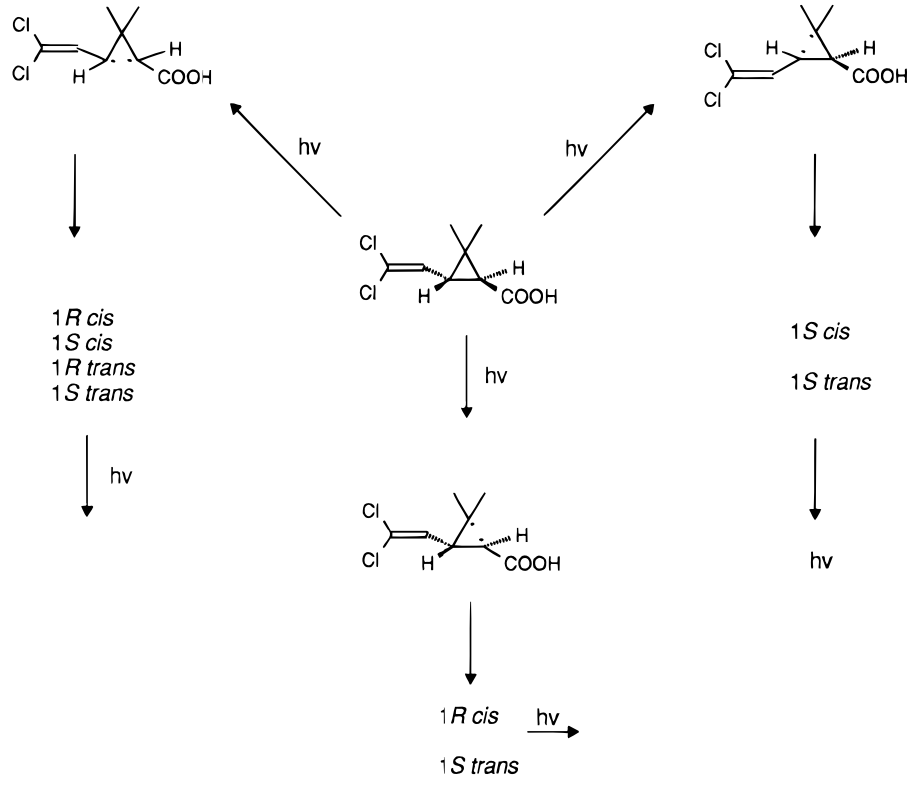


Fig. 12. Photoisomerisation of (1*S*)*trans*-permethric acid.

transfluthrin could become an interesting material in insect resistance management practices.

Feedback from users of cyfluthrin (**9,** Table 8) in areas where pyrethroid resistance was appearing in cotton pests, indicated that good control was still achievable with cyfluthrin, and even better control with the active-isomer-enriched high-*trans* beta-cyfluthrin (**35,** Table 8). Laboratory tests confirmed this observation[41,42] which was corroborated by the author's colleague Wolfgang Leicht in our entomological institute in Monheim.[43]

The intrinsic role of the *para*-fluorine substituent in cyfluthrin, which has a twofold greater activity and more favourable resistance factors than cypermethrin

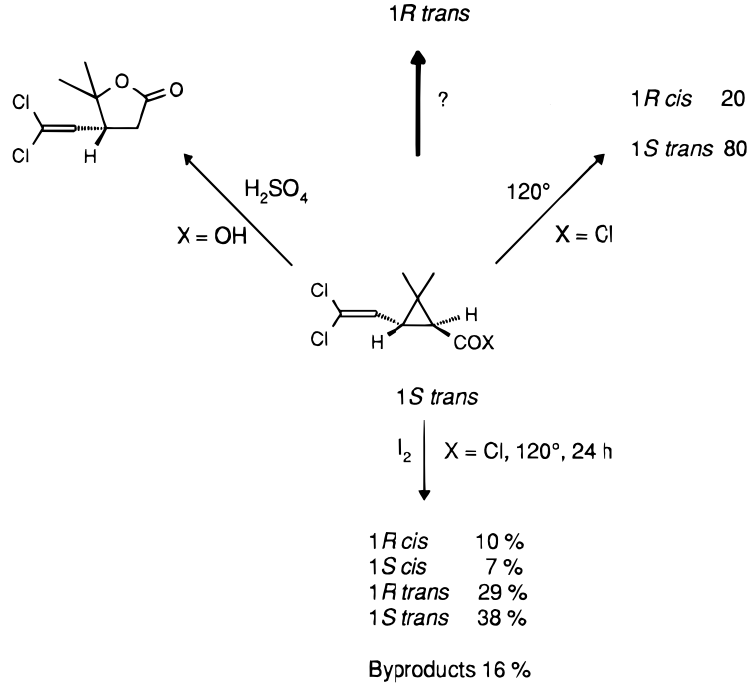


Fig. 13. Isomerisations of (1*S*)*trans* permethric acid.

(**7,** Table 2), was a matter of great interest not only for us. It was suspected that the mode of detoxification by resistant insects should be implicated, in that cyfluthrin, and particularly the *trans*-isomer, is less prone than cypermethrin to detoxification by resistant insects. Theoretical calculations and experimental results[44] indicated that the preferred sites for hydroxy radical attack on the *meta*-phenoxybenzyl system were the two carbon atoms adjacent to the oxygen bridge between the two phenyl groups, followed by the *o*′- and *p*′-positions. A fluorine atom adjacent to this carbon should drastically influence this reaction. However, the observed positions of metabolic hydroxylation[45] do not support the hypothesis of a radical hydroxylation mechanism. Hydroxylation of the phenyl group, as one main detoxification route in cypermethrin and cyfluthrin,[46] takes place mainly at the *p*′-position. The other important route to detoxification is ester cleavage (Fig. 14), which can occur both in the classical hydrolytic fashion and by oxidation of the benzylic hydrogen, yielding a very labile derivative of *m*-phenoxybenzoic acid or by hydration of the CN group. Many such bond breakings around this benzylic carbon atom could be imagined to be influenced electronically by the 4-fluorine atom to explain the differential behaviour *in vivo* between the phenoxy- and fluorophenoxypyrethroid. But quantum mechanical calculations by Michael Schindler in our institute in 1993 (unpublished) revealed no difference at all between the two alcohol components with respect to bonds around that benzylic carbon atom. Thus, cyfluthrin does not seem to have an intrinsically higher metabolic stability than cypermethrin with respect to ester cleavage or hydroxylation by an oxidase or to hydration of the CN group by a nitrilase.

Calculations of the electrostatic potential of both moieties revealed distinct differences in one part of the molecule where the fluorine is situated (M. Schindler, 1993, unpublished). In this area a significantly protruding negative potential in the extension of the C–F bond causes an attraction towards a positive charge. Thus, introduction of a fluorine in this specific position may explain the increased insecticidal activity resulting from fluorination of cypermethrin, as well as the suspected retarded detoxification of cyfluthrin by resistant insects, in that attraction between fluorine and a putative positive charge at the pyrethroid binding site would lead to enhanced binding and thus to enhanced activity. Repulsive forces caused by fluorine towards a putative negative charge, as a result of a mutation at the recognition

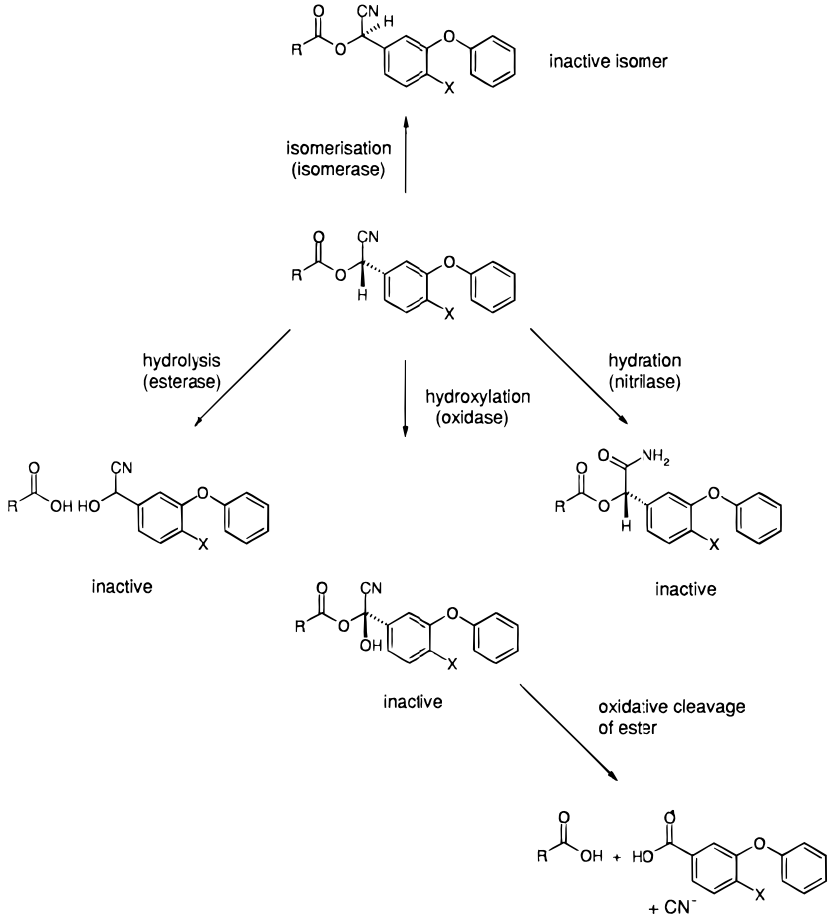


Fig. 14. Possible detoxification of cypermethrin and cyfluthrin around the benzylic carbon atom.

site of a metabolising enzyme of a resistant insect, explain reduced recognition and thereby reduced detoxification.

Contrary to the observations in most cases with biologically active compounds that exchange of a fluorine atom for a chlorine substituent does not totally change the biological activity, the 4-chloro analogue of cyfluthrin is only weakly active. This hints at the important contribution of a specific conformation of the *meta*-phenoxybenzyl system, which is not available with the chloro substituent which has a larger 'van der Waals' radius than fluorine, but a similar electrostatic radius of action.

Data from thorough biological experiments, which are difficult to carry out, could allow a more sound explanation. The electrophysiological differences at the single sodium channel of a nerve e.g. of a sensitive and a resistant larva of *Plutella maculipennis* Curt. between the pure single active isomers of cypermethrin and cyfluthrin (i.e. (1*R*)*cis* α*S* and (1*R*)*trans* α*S* isomers) have not been investigated yet to my knowledge. Data comparing the metabolism of these isomers in living sensitive and resistant caterpillars as well as investigations of the *in-vitro* metabolism with the degrading enzymes from these organisms would extend the experimental basis for understanding. In the absence of those data, any explanation of the specific influence of that peculiar fluorine atom in ester-, ether- and hydrocarbon pyrethroids distinguished by the 4-fluoro-3-phenoxy moiety will remain speculation.

7 CONCLUSIONS

Even in this modern age of random screening of the many products of combinatorial chemistry there is a continuing need for a constant search for new chemistry, new reagents, new reactions and new analytical techniques. It is the author's deep conviction that chemists, having a 'personal' relation with molecules, their shapes, properties and behaviour, and being able to crosslink even seemingly unrelated observations will still play a dominant role in future discovery processes of biologically active compounds. They must also have a good knowledge and imagination of 'biological chemistry' and there must be a very close, cooperative working relationship between chemists and biologists and those in other allied disciplines, notably for the exchange and discussion of observations and surprises. This combination will surely lead to new discoveries within the risky voyage in the insecticidal structure–activity archipelago imagined as Fig. 15.

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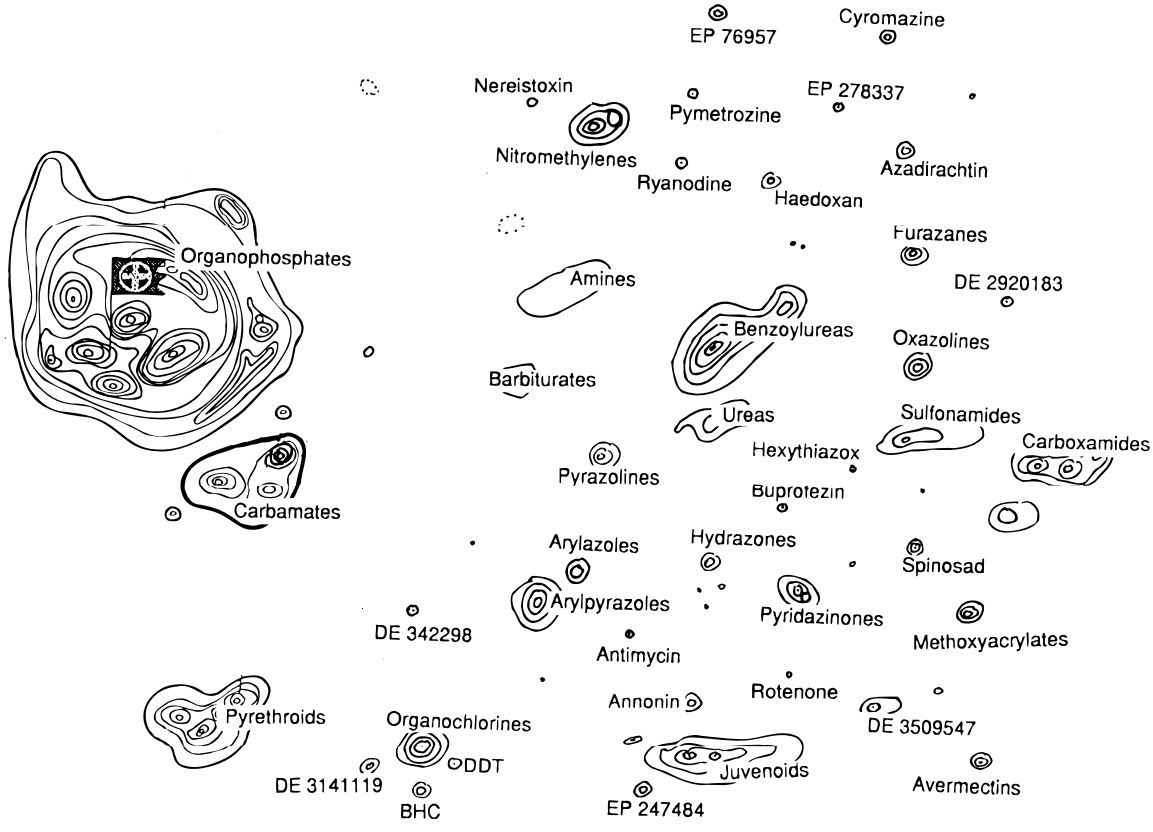

Fig. 15. The insecticidal structure activity archipelago.

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